Remarks

Response to Notice of Non-Compliant Amendment

This paper is identical to the response filed March 23, 2006 except that it indicates cancellation of claims 1-26.

Support for the New Claims 62 and 63

The specification supports new claims 62 and 63 at page 10, lines 22-24: "According to another embodiment of the invention, interference with the expression of MDM2 provides a therapeutic modality. The method can be applied in vivo, in vitro, or ex vivo." The new claims do not add new matter.

The Rejection of Claims 27, 28 and 56 Under 35 U.S.C. § 112 ¶ 1

Claims 27, 28, and 56 are rejected under 35 U.S.C. § 112 ¶ 1 as neither described nor enabled. Applicants respectfully traverse the rejections. Applicants also traverse the rejections as they may be applied to new claims 62 and 63.

Written Description

Each of pending claims 27, 28, 56, 62, and 63 recites a genus of antisense oligonucleotides which are complementary to human MDM2 mRNA. The antisense oligonucleotides of claims 27, 28, and 56 "inhibit transcription or translation of a human MDM2 gene." The antisense oligonucleotides of claims 62 and 63 "interfere with expression" of MDM2 The Patent Office asserts that the specification does not adequately describe the oligonucleotides

of claims 27, 28, and 56 because the specification does not explicitly disclose a sufficient number of representative species of antisense oligonucleotides which have the recited function.[1]

An explicit description of individual species is not the only way a specification can describe a recited genus:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics . . . .

The U.S. Patent and Trademark Office's Written Description Guidelines, 66 Fed. Reg. 1099, 1106 (January 5, 2001) (internal references omitted), cited with approval in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). The present specification meets the written description requirement because it describes the recited antisense oligonucleotides by way of "relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties." *Id.*

A specification is directed to those skilled in the art. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d. 1555, 1563-1564, 19 U.S.P.Q. 1111, 1115 (Fed. Cir. 1991). Thus, the U.S. Patent and Trademark Office must consider the knowledge of those skilled in the art when determining whether a specification meets the written description requirement. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989). The present specification teaches both the coding sequence of human *MDM2* (including the start and stop codons) and its 5′ untranslated region (UTR) (see Figure 1). At this application's April 7, 1992 priority date, those skilled in the art were well aware of the rules of complementary base pairing (*i.e.*, A is complementary to

[1] Final Office Action at page 6 ¶ 2.

T and G is complementary to C). With this knowledge and with the *MDM2* sequence provided in the specification, it would be an easy (even if time consuming) task for a skilled worker to envision every possible antisense oligonucleotide which is complementary to any portion of the disclosed sequence. The specification therefore inherently describes to those skilled in the art a vast number of antisense oligonucleotides which have the relevant identifying characteristic of being complementary to human *MDM2* mRNA, as recited in the pending claims.

The Examiner contends the specification must explicitly describe particular antisense oligonucleotides because only a very few *MDM2* antisense oligonucleotides actually would function to inhibit transcription or translation of a human *MDM2* gene, as recited in claims 27, 28, and 56.[2] The Examiner cites no relevant evidence to support this contention. In fact, post-filing date experience demonstrates that just the opposite is true: *MDM2* antisense oligonucleotides actually tested do inhibit mRNA expression. For example:

- Capoulade[3] used an antisense oligonucleotide (5′-GTTGGTATTGCACAT-3′) complementary to human *MDM2* to inhibit translation of the MDM2 gene in Burkitt lymphoma cells, which overexpress human MDM2.
- Chen[4] used an antisense oligonucleotide (5′-GATCACTCCCACCTTCAAGG-3′) complementary to human *MDM2* to inhibit MDM2 expression in JAR (choriocarcinoma) and SJSA

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[2] Paragraph bridging pages 6 and 7 of the Final Office Action.

[3] Capoulade *et al.*, "Apoptosis of tumoral and nontumoral lymphoid cells is induced by both mdm2 and p53 antisense oligodeoxynucleotides," *Blood 97* (2001):1043-1049. See page 1044, col. 1, lines 14-15, and page 1047, col. 1, lines 33-35.

[4] Chen *et al.*, "Synergistic activation of p53 by inhibition of *MDM2* expression and DNA damage," *Proc. Natl. Acad. Sci. USA 95* (1998):195-200. See page 195, column 2, lines 23-26.

(osteosarcoma) cells, both of which overexpress human *MDM2*. Sato[5] and Goetz[6] used the same antisense oligonucleotide to inhibit MDM2 expression *in vitro* in U2-OS osteosarcoma cells and in murine pre-B lymphocyte cell lines, respectively.

- Wang[7] used an antisense oligonucleotide (5′-UGACACCTGTTCTCACUCAC-3′) complementary to human *MDM2* to inhibit MDM2 expression in neoplastic SJSA cells *in vitro*. Zhang[8] used the same antisense oligonucleotide to inhibit MDM2 expression *in vitro* in prostate cancer cell lines LNCaP, DU145, and PC3.
- Miraglia[9] used an antisense oligonucleotide (5′-AGCTTCTTTGCACATGTAAA-3′) complementary to human *MDM2* to inhibit *MDM2* expression in the human neoplastic lung carcinoma cell line A549 *in vitro*.

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[5] Sato *et al.*, "Enhancement of Drug Induced Apoptosis by Antisense Oligodeoxynucleotides Targeted against Mdm2 and $p21^{WAF1/CIP1}$," *Anticancer Research 20*, 837-42, 2000.

[6] Goetz *et al.*, "Requirement for Mdm2 in the Survival Effects of Bcr-Abl and Interleukin 3 in Hematopoietic Cells," *Cancer Res. 61*, 7635-41, October 15, 2001

[7] Wang *et al.*, "MDM2 oncogene as a target for cancer therapy: An antisense approach," *Int. J. Oncol. 15* (1999):653-660. See page 655, column 2, line 20 to page 656, column 1, line 2.

[8] Zang *et al.*, "Antisense therapy targeting MDM2 oncogene in prostate cancer: Effects on proliferation, apoptosis, multiple gene expression, and chemotherapy," *Proc. Natl. Acad. Sci. USA 100*, 11636-41, September 30, 2003¶.

[9] Miraglia *et al.*, "Antisense Oligonucleotide Modification of Human MDM2 Expression," U.S. Patent No. 6,238,921. See Tables 1 and 3.

- Fiddler[10] used a full-length antisense oligonucleotide complementary to human *MDM2* cDN A to inhibit MDM2 expression in C2C12 cells, a myoblast cell line which overexpresses MDM2.

The post-filing date references described above demonstrate that identification of antisense oligonucleotides which function to inhibit human *MDM2* mRNA expression is not a rare event. Chen reports screening nine oligonucleotides.[11] In another publication, Zhang and Wang report screening "more than 12" oligonucleotides and found activity in more than one of them ("In the design of anti-MDM2 oligos, more than 12 oligos were initially tested and significant difference in activity was found.")[12] The experiments described in the references used techniques for synthesizing, stabilizing, and administering the oligonucleotides to cells which were well known in the art at this application's 1992 priority date (see below).

When the knowledge of persons skilled in the art is properly considered, the specification rebuts the unsupported contention that functional oligonucleotides would be rare and indicates to those persons that Applicants invented the subject matter recited in the pending claims as of the application's April 7, 1992 priority date. These arguments apply with equal force to new claims 62 and 63.

Enablement

Claims 27, 28, 56, 62, and 63 are directed to *in vitro* methods of interfering with expression of MDM2. The methods comprise administering an antisense oligonucleotide which

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[10] Fiddler *et al.*, "Amplification of *MDM2* Inhibits MyoD-Mediated Myogenesis," *Mol. Cell. Biol. 16,* 5048-57, September 1996. See page 5053, paragraph bridging cols. 1 and 2.

[11] Page 195, col. 2, last full paragraph.

[12] Zang & Wang, "Antisense Oligonucleotide Inhibitors of MDM2 Oncogene Expression," in Methods in Molecular Medicine 85: Novel Anticancer Drug Protocols, pages 205-22, Buolamwini & Adjei, eds., Humana Press, 2003, at page 218, col. 1, last paragraph.

is complementary to human MDM2 mRNA *in vitro* to a neoplastic cell (claims 27, 28, and 62) or to a cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA, or elevated expression of human MDM2 protein (claims 56 and 63). Claims 27, 28, and 56 recite administration of the oligonucleotides in an amount effective to inhibit transcription or translation of a human MDM2 gene. New claims 62 and 63 recite administration of the oligonucleotides in an amount effective to interfere with expression of MDM2. None of the claims requires any particular level of interference or interference. New claims 62 and 63 do not require that the interference occur by any particular mechanism.

To be enabling, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without resort to undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). This requirement, however, has never been interpreted to mean that the specification must enable every embodiment within the scope of the claims. *See, e.g., In re Wright*, 999 F.2d 1557, 1563, 27 U.S.P.Q.2d 1510, 1515 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d at 496, 20 U.S.P.Q.2d at 1445 ("It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.") (citation omitted). Rather, "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

The Advisory Action explains that the basis of the enablement rejection is that identification of antisense oligonucleotides which will inhibit transcription or translation of a human *MDM2* gene "would have [ ] required undue experimentation, based on the art recognized unpredictability of antisense gene inhibition of a given gene, in cells in vitro at the time the

instant invention was made given only the primary nucleotide coding sequence of that gene."[13] Whether any screening would be undue must be considered in the context of the particular technology involved:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citations and footnote omitted).

The enablement rejection in *Wands* was based in part on the PTO's assertion that an undue amount of screening would be required to identify an antibody with particular characteristics recited in Wands' claims. Wands made 143 hybridomas and screened nine of these hybridomas beyond the initial screen for antigen binding. *Id.* at 739, 8 U.S.P.Q.2d at 1405. The court understood that screening in the art of making monoclonal antibodies was routine:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Id. at 740, 8 U.S.P.Q.2d at 1406. The nature of antisense technology, too, is that it involves screening oligonucleotides to determine which ones have the desired function. Those skilled in the art expect to do this screening and would therefore find it routine, not undue. Chen screened nine oligonucleotides. Zang screened 12 oligonucleotides. Screening merely 9 or 12 oligonucleotides does not rise to the level of undue experimentation. That some experimentation

[13] Page 2 of the Advisory Action mailed December 29, 2005.

may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The test is not merely quantitative, because a considerable amount of experimentation is permissible if the experimentation is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

In any event, as discussed above, post-filing date experience with antisense *MDM2* oligonucleotides indicates it is not at all a rare event to identify oligonucleotides with the desired activity. There is a wealth of post-filing date evidence that teaches *in vitro* methods of inhibiting expression of *MDM2* mRNA in a variety of neoplastic cells or cells which overexpress human *MDM2*.[14] See Capoulade, Chen, Sato, Goetz, Wang, Zang, Miraglia, and Fiddler, discussed above. See also the review by Bartel *et al.*, "*MDM2* and Its Splice Variant Messenger RNAs: Expression in Tumors and Down-Regulation Using Antisense Oligonucleotides," *Mol. Cancer Res. 2*, 29-35, January 2004, at page 34: "MDM2-AS-ODNs specifically inhibit MDM2 expression . . . ."

The Examiner contends that these post-filing date references "appear to provide post-filing disclosures that are significantly more detailed than the disclosure of the specification; i.e., that are not commensurate in scope with the instantly filed specification."[15] But the experiments reported in each of these references used oligonucleotide technology that was known in the art when this application was filed:

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[14] To support enablement of a claimed invention, applicants may submit post-filing date evidence that demonstrates that the claimed invention works. M.P.E.P. § 2164.05.

[15] Page 2 of the Advisory Action mailed December 29, 2005.

- Capoulade's oligonucleotides had phosphorothioate backbones (page 1044, col. 1, lines 48-52) and were delivered using electroporation (page 1044, col. 2, lines 3-5).
- Chen's oligonucleotides had phosphorothioate backbones (page 197, col. 1, lines 5-8) and were delivered using a lipid (Lipofectin) complex (page 196, col. 1, lines 12-15).
- Sato's oligonucleotides had phosphorothioate backbones (page 838, col. 1, third paragraph) and were delivered using a cationic lipid transfection reagent Transfast (*Id.*);
- Goetz's oligonucleotides had phosphorothioate backbones (page 7636, col. 2, first full paragraph) and were delivered using electroporation (*Id.*).
- Wang's oligonucleotides had a mixed backbone (page 654, col. 2, lines 51-54) and were delivered using Lipofectin (page 655, col. 1, lines 17-18).
- Zang's oligonucleotides had 2′-methoxyethoxy modifications (page 11636, col. 2, last paragraph) and were delivered using Lipofectin (page 11637, col. 1, first paragraph).
- Miraglia's oligonucleotides had phosphorothioate backbones (col. 16, lines 9-12) and 2′-methoxyethoxy modifications (col. 17, lines 24-27) and were delivered using Lipofectin (col. 18, lines 2-4).
- Fiddler used an *MDM2* cDNA cloned in the antisense orientation (page 5053, col. 1, last paragraph) and delivered it using Lipofectamine (page 5048, col. 2, third full paragraph).

Each of these technologies was known and used in the art before this application was filed. See Watson[16] and Woolf[17] (phosphorothioate backbones); Hambor[18] (delivery of oligonucleotides using electroporation); Burch & Mahan[19] (delivery of oligonucleotides using lipid complexes); and Dagle[20] and Ulmann & Peyman[21] (mixed backbone and 2'-methoxyethoxy modifications). Use of after-filing date technology is not apparent in any of Capoulade, Chen, Sato, Goetz, Wang, Zang, Miraglia, or Fiddler. These references are direct, relevant evidence that the disclosure of this specification is enabling.

The Final Office Action and the Advisory Action cited four references which purportedly support the enablement rejection: James, Branch, Rojanaskul, and Agrawal.[22] But these references are not directly related to the claimed subject matter. As the Examiner points out, "the claims in the instant Applicant are drawn to methods of inhibiting the expression of a particular gene, the human MDM2 gene, *in vitro*, in a cell."[23] Not one of James, Branch, Rojanaskul, or Agrawal contains any discussion of using antisense oligonucleotides to interfere

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[16] Watson *et al.*, *Cancer Res. 51*, 3996-4000, August 1991 (abstract); see lines 3-6.

[17] Woolf *et al.*, *Nucl. Acids Res. 18*, 1763-69, 1990 (*e.g.*, page 1764, col. 1, first full paragraph).

[18] Hambor *et al.*, *Proc. Natl. Acad. Sci. USA 85*, 4010-14, June 1988; see page 4011, col. 1, lines 40-45.

[19] Burch & Mahan, *J. Clin. Investigation, Inc. 88*, 1190-96, October 1991; see page 1191, col. 1, lines 24-35).

[20] Dagle *et al.*, *Nucl. Acids Res. 19*, 1805-10, 1991 (*e.g.*, page 1805, abstract).

[21] Ulmann & Peyman, *Chemical Review 90*, 544-84, June 1990; see page 558, col. 2, lines 20-23.

[22] James, *Antiviral Chemistry and Chemotherapy 2*, 191-214, 1991; Branch, *TIBS 23*, 45-50, 1998; Rojanaskul, *Adv. Drug Deliv. Reviews 18*, 115-31, 1996; and Arawal & Kandimalla, *Mol. Med. Today 6*, 72-81, February 2000.

[23] Final Office Action at page 13, last paragraph.

with expression of MDM2 in a cell *in vitro*. In contrast, Applicants' evidence discussed above is directly probative.

Moreover, the references must be considered in their entireties. First, each of the references is largely concerned with *in vivo* use. Difficulties which may be relevant for *in vivo* use (side effects, levels, targeting, etc.) are not relevant to the pending claims, which recite *in vitro* administration to a cell. Large portions of the discussions in the cited references are therefore not even relevant to administration of antisense oligonucleotides *in vitro*.

In fact, rather than supporting the enablement rejection, the cited references actually demonstrate that those skilled in the art in 1992 had a vast array of knowledge and many options for selecting oligonucleotides, modifying them, enhancing their uptake, and the like. *See, e.g.*, Rojanaskul at pages 119-23. This evidence weighs in favor of enablement, not against it. See also James, whose review of the antisense literature concluded:

> The literature is now well populated by experiments in which antisense RNA has been used to inhibit the expression of a gene, the replication of a virus or to modify the phenotype of cells. I summarize the main features of these in Table 1. The variety of target systems, methods of delivery, assay methods and styles of publication make a systematic comparison, general conclusions about the mechanism of antisense action or the optimal method of antisense delivery somewhat difficult. *Two generalizations may be made at the outset: that artificial inhibition is achievable in a wide variety of organisms and their constituent cells and that seemingly any gene is susceptible.*

Page 194, col. 1, first full paragraph (emphasis added).

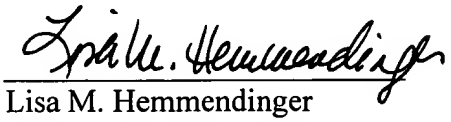
All the evidence of record must be considered in its entirety. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). The specification explicitly teaches how to carry out the claimed methods. The Examiner provides no reasonable basis to doubt the claimed methods' operability or enablement or to counter Applicants' arguments and evidence of

record. Properly considered in its entirety, the evidence of record in this application weighs in favor of enablement.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
BANNER & WITCOFF, LTD.

Dated: April 5, 2006

By: 
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